Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD): Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Heterozygous Familial Hypercholesterolemia (HeFH)

- HeFH is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) and, if untreated, is associated with significant premature cardiovascular morbidity and mortality.[1-2]
- HeFH is most commonly due to loss-of-function mutations in the LDL receptor gene.[3]
- Current treatments (statins, ezetimibe, bile acid sequestrants, niacin) yield reductions in LDL-C of 50-65% in HeFH patients. However, many patients are still unable to achieve recommended LDL-C targets.[4]

1. Slack J. *Lancet*. 1969;2:1380-2.
2. Goldstein JL, et al, eds. *Familial hypercholesterolemia*. 8th Edition; 2001.
3. Leigh SE, et al. *Ann Human Genet*. 2008;72:485-98.
4. Stein EA, et al. *J Clin Lipidol*. 2007;1:280-6.

Background: PCSK9 Inhibition and AMG 145

- LDL-C clearance from the circulation is mostly regulated by LDL receptors (LDLRs) on hepatocytes, which bind LDL-C and deliver it to the cell via endocytosis.[1]
- LDLRs are then either degraded or recycled back to the cell surface.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the LDLR, along with LDL, and targets it for degradation, thereby reducing LDLR recycling with resultant increased serum LDL-C.
- AMG 145 is a fully human monoclonal antibody that binds to PCSK9 and blocks its interaction with LDLRs.

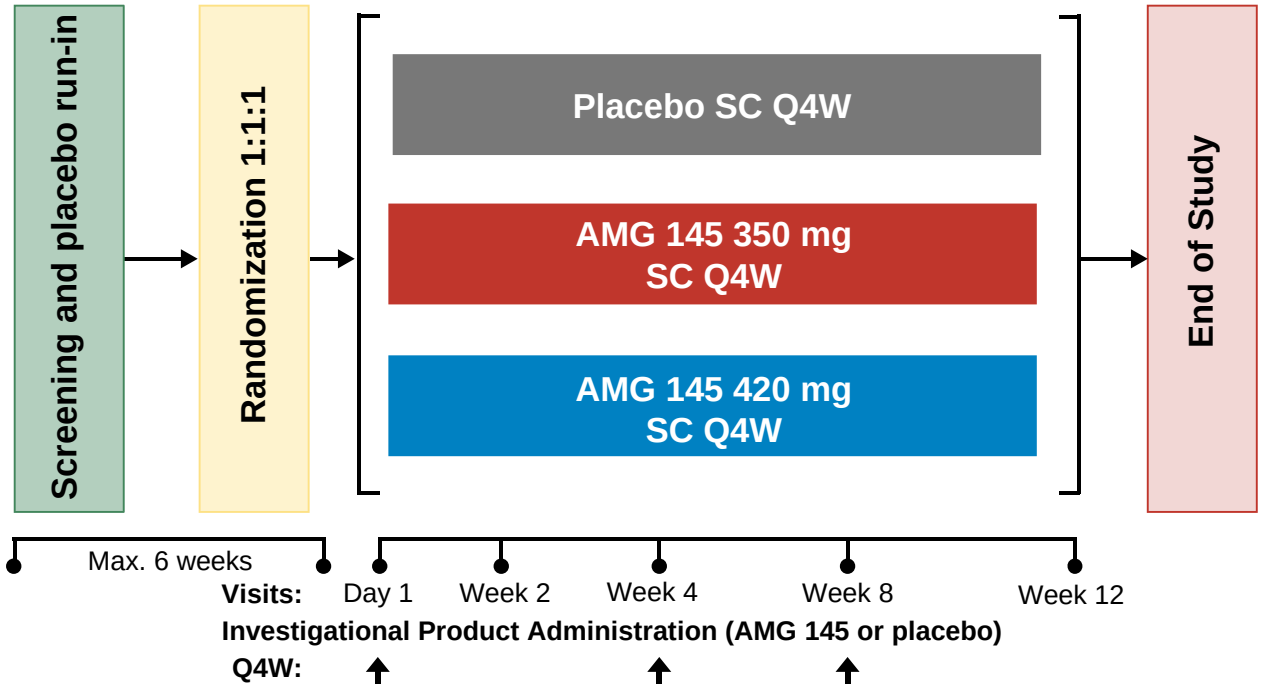
1. Cohen JC, et al. *N Engl J Med.* 2006;354:1264-72.

RUTHERFORD Background

- **R**ed**u**ction of LDL-C with PCSK9 Inhibi**t**ion in **He**te**r**ozygous **F**amilial Hyperch**o**leste**r**olemia **D**isorder
- Global, Randomized, Double-blind, Placebo-controlled
- **Study objective:**

  Evaluate the efficacy and safety of AMG 145 350 mg and 420 mg administered subcutaneously (SC) every 4 weeks (Q4W) in a large and diverse cohort of HeFH patients unable to achieve an LDL-C < 100 mg/dL despite statin therapy with or without ezetimibe

RUTHERFORD: Study Design



Primary endpoint: % change in LDL-C, *measured by ultracentrifugation*, from baseline at 12 weeks

Q4W, every 4 weeks; SC, subcutaneous

Population

- 18−75 years, with a diagnosis of HeFH by Simon Broome criteria
- LDL-C ≥ 100 mg/dL and triglycerides ≤ 400 mg/dL
- At least 4 weeks of stable lipid-lowering therapy (eg, statin, ezetimibe, bile-acid sequestants, niacin)

RUTHERFORD: Baseline Characteristics

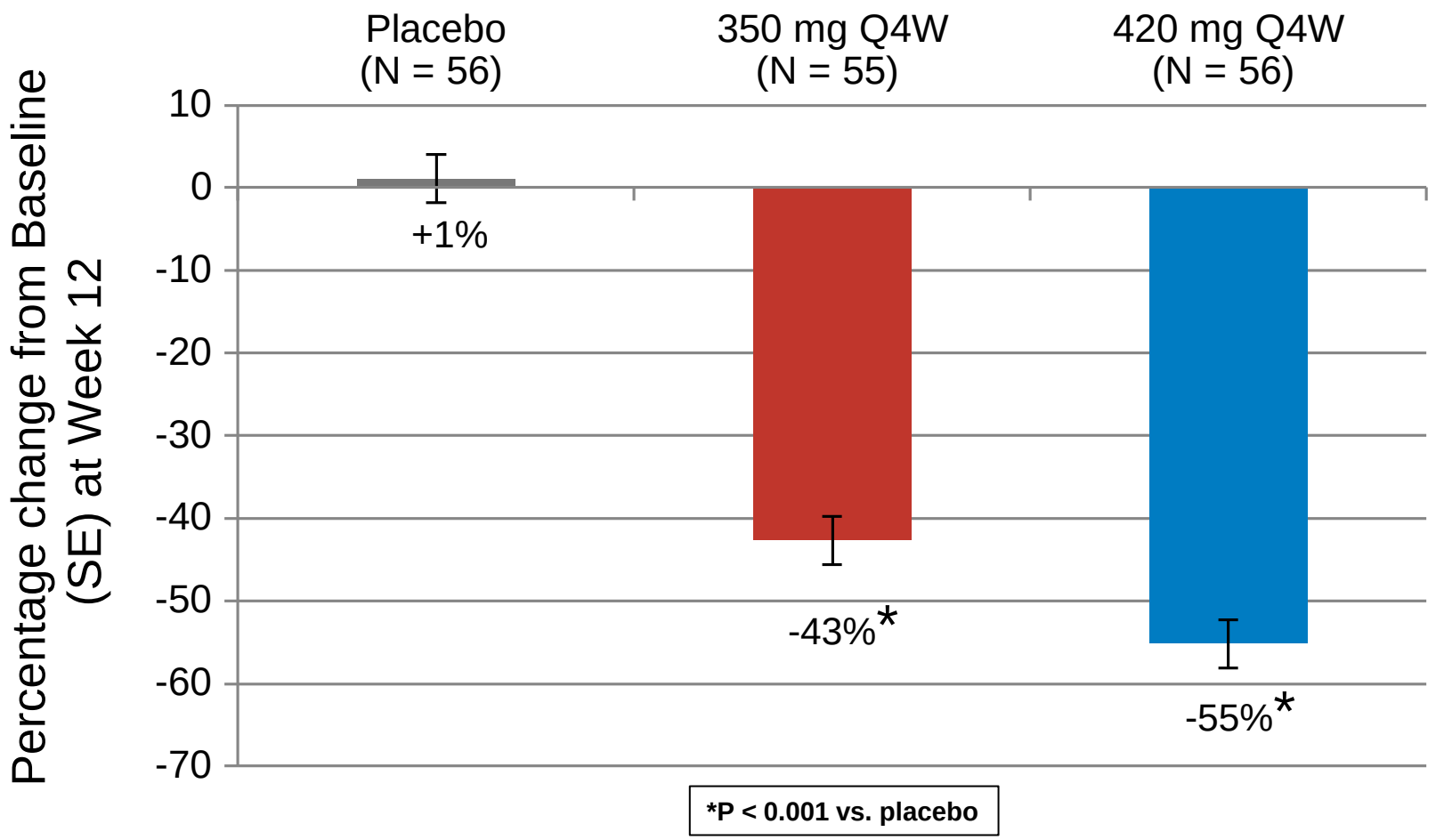
Characteristic	Placebo N = 56	AMG 145 350 mg Q4W N = 55	AMG 145 420 mg Q4W N = 56
Sex, male, n (%)	24 (43)	30 (55)	35 (63)
Age, years, mean (SD)	49 (11)	48 (14)	52 (13)
Race, white, n (%)	48 (86)	48 (87)	52 (93)
LDL-C, mg/dL, mean (SD) *	161 (44)	157 (46)	150 (36)
Total cholesterol, mg/dL, mean (SD)	234 (50)	225 (50)	219 (43)
Triglycerides, mg/dL, mean (SD)	123 (73)	122 (80)	124 (65)
Lp(a), nmol/L, median (Q1, Q3)	45 (13, 155)	36 (10, 137)	40 (15, 178)
Free PCSK9, ng/mL, mean (SD)	600 (175)	596 (179)	605 (192)
Lipid-lowering therapy, n (%)	56 (100)	55 (100)	56 (100)
Intensive statin use, n (%) ‡	49 (88)	52 (95)	49 (88)
Ezetimibe use, n (%)	36 (64)	36 (65)	36 (64)

*LDL-C measured by ultracentrifugation

‡ Defined as simvastatin 80 mg QD, atorvastatin $\geq$ 40 mg QD, rosuvastatin $\geq$ 20 mg QD, or any statin plus ezetimibe

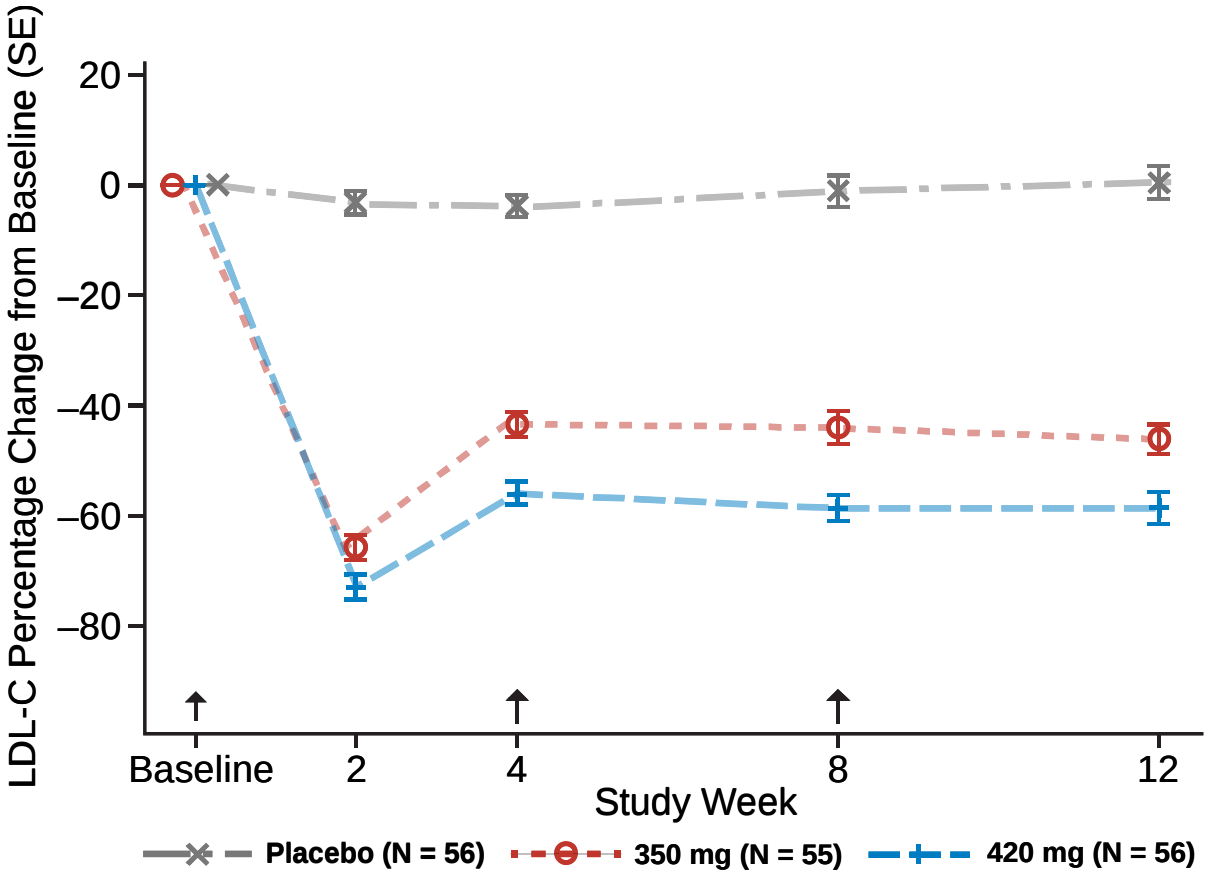
SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; Lp(a), Lipoprotein (a)

RUTHERFORD: % Change in LDL-C, by UC, from Baseline to Week 12



Q4W, every 4 weeks; SE, standard error; UC, ultracentrifugation
LDL-C values at baseline and week 12 were measured using preparative UC.
Least Square Means are presented from the ANCOVA model including treatment and stratification factors as covariates.
Missing UC LDL-C values at week 12 were imputed using last observation carried forward and calculated LDL-C. A Hochberg adjustment was used to control the family wise error rate at ≤ 0.05.

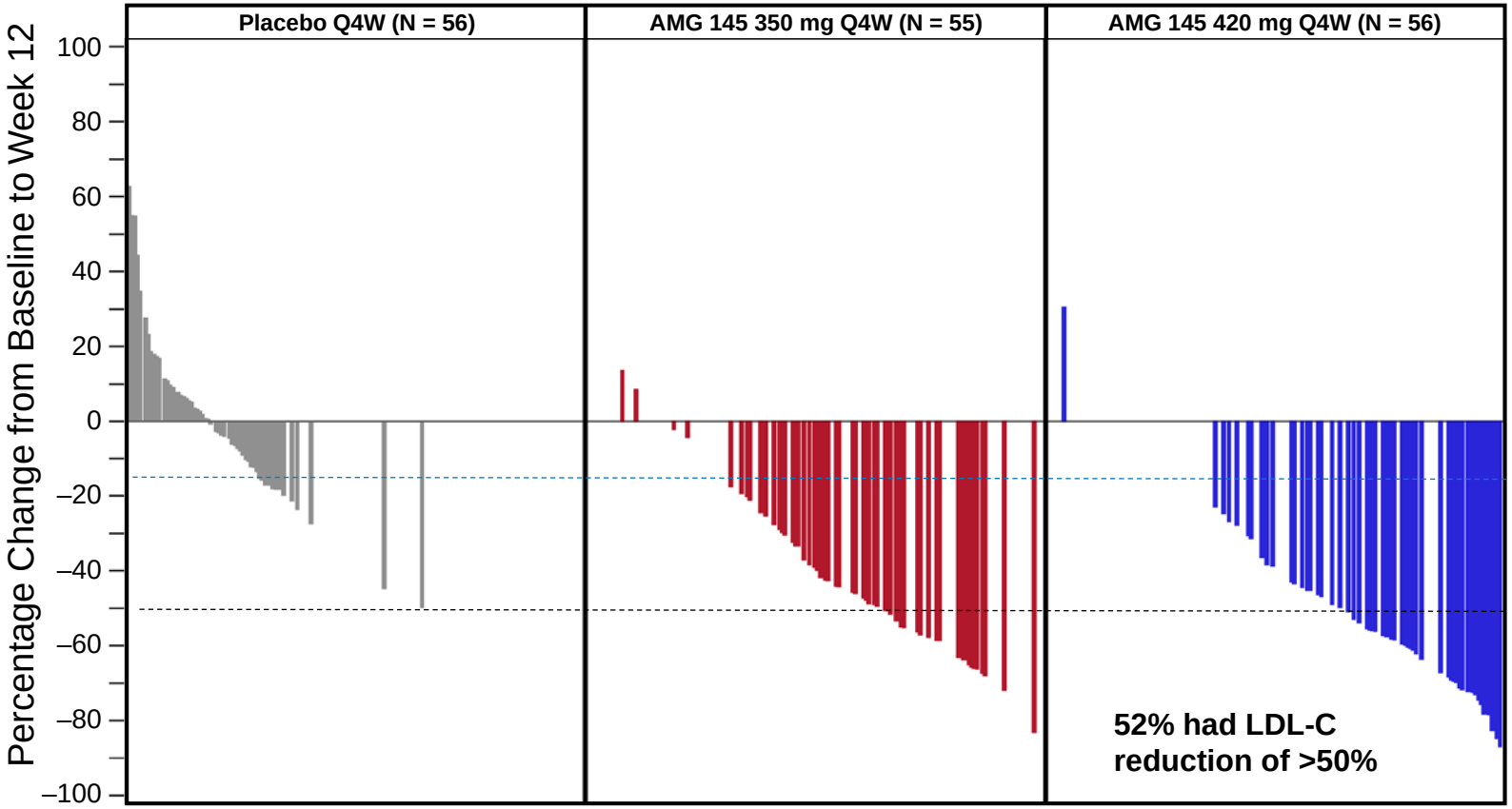
RUTHERFORD: LDL-C Changes During Treatment



LDL-C based on Friedewald calculation

↑ Investigational product administration

RUTHERFORD: % Change in LDL-C, by UC, from Baseline to Week 12 for Individual Patients



5 patients (AMG 145) were considered poor responders (< 15% LDL-C reduction) from baseline at Week 12.

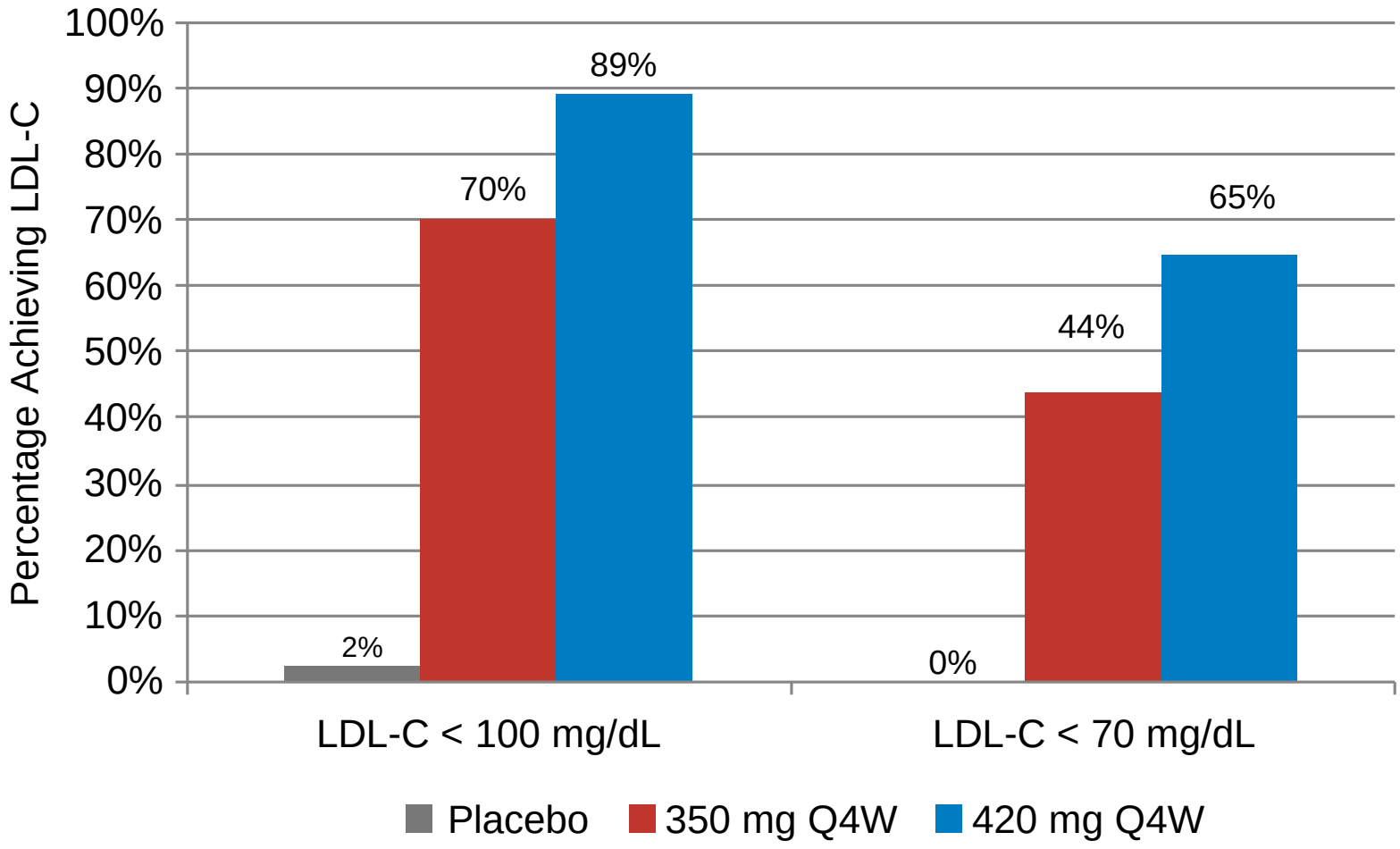
UC, ultracentrifugation

RUTHERFORD: LDL-C Profile of Poor Responders (< 15% Reduction at Week 12)

Patient	AMG 145 Dose	# Of Doses	Calculated LDL-C mg/dL (% change from baseline)				
			Baseline	Week 2	Week 4	Week 8	Week 12
1	350 mg	Received 1 dose	152 (NA)	65 (-57%)	122 (-19%)	148 (-2%)	148* (-2%)
2	350 mg	Completed all 3 doses	151 (NA)	62 (-59%)	54 (-64%)	76 (-50%)	177 (+17%)
3	350 mg	Completed all 3 doses	169 (NA)	27 (-84%)	98 (-42%)	99 (-41%)	178 (+5%)
4	350 mg	Completed all 3 doses	168 (NA)	99 (-41%)	137 (-18%)	165 (-1%)	155 (-7%)
5	420 mg	Received 1 dose	95 (NA)	35 (-63%)	61 (-36%)	95 (0%)	125 (+32%)

* Last observation carried forward

RUTHERFORD: % of Patients Achieving LDL-C, by UC, Targets at Week 12



UC, ultracentrifugation

RUTHERFORD: Effect of AMG 145 on Other Lipid Parameters Compared to Placebo

Treatment Difference Versus Placebo, mean (SE)	AMG 145 Q4W	
	350 mg N = 55	420 mg N = 56
ApoB, %	-35 (4) *	-46 (4) *
Total cholesterol, %	-31 (3) *	-40 (3) *
VLDL-C, %	-25 (10) ‡	-36 (10) *
Non-HDL-C, %	-42 (4) *	-53 (4) *
Triglycerides, %	-15 (6) †	-20 (6) *
HDL-C, %	8 (3) †	7 (3) †
ApoA1, %	2 (2)	2 (2)
Lp(a) , %	**-23 (4) ***	**-31 (4) ***

*P<0.001; †P <0.01, ‡ P<0.05
Treatment differences are based on ANCOVA model including treatment group and stratification factors as covariates.
Missing values at week 12 were imputed using last observation carried forward.

RUTHERFORD: Safety and Tolerability

Adverse Events, Patient Incidence, n (%)	Placebo N = 56	AMG 145	
		350 mg N = 55	420 mg N = 56
Treatment-emergent AEs	33 (58.9)	32 (58.2)	37 (66.1)
Most common AEs			
Nasopharyngitis	6 (10.7)	7 (12.7)	7 (12.5)
Injection site pain	1 (1.8)	5 (9.1)	2 (3.6)
Headache	5 (8.9)	3 (5.5)	3 (5.4)
Serious AEs	0 (0)	0 (0)	2 (3.6)
Deaths	0 (0)	0 (0)	0 (0)
Treatment-related AEs	6 (10.7)	13 (23.6)	8 (14.3)
AEs leading to discontinuation	1 (1.8)	1 (1.8)	1 (1.8)
Muscle-related AEs	2 (3.6)	2 (3.6)	4 (7.1)
Injection-site reactions	3 (5.4)	6 (10.9)	2 (3.6)

AE, Adverse event
Some patients experienced more than 1 AE.

RUTHERFORD: Serious Adverse Events

- **Two patients (AMG 145 420 mg group)**
  - **Atrial fibrillation:** A 65-year-old Caucasian female with a history of angina, coronary artery bypass graft, hypertension, ex-smoker, and repeat coronary catheterizations experienced atrial fibrillation 15 days after first dose of investigational product. Patient was discharged same day in stable condition.
  - **Acute appendicitis, post-operative wound infection:** A 33-year-old Caucasian male had an episode of acute appendicitis ~ 2 months after the first dose of investigational product followed by post-operative wound infection ~ 1 week later which resolved following antibiotic therapy.
- **None were considered treatment-related by the investigator.**
- **Blinded investigational product was continued for both patients.**

RUTHERFORD: CK Elevations

CK Elevations at Any Post-Baseline Visit	Placebo N = 42	AMG 145	
		350 mg N = 50	420 mg N = 50
> 5xULN, n (%)	0 (0)	1 (2)	2 (4)
> 10xULN, n (%)	0 (0)	0 (0)	1 (2)

- 1 patient in the 350 mg group and 1 patient in the 420 mg group had an elevation > 5xULN and ≤ 10xULN at any post-baseline visit
- 1 patient in the 420 mg group had an elevation > 10xULN at Week 8
- All were asymptomatic, single occurrences related to strenuous exercise that resolved spontaneously without discontinuation of investigational product.

CK, creatine kinase
ULN, Upper limit of normal
The table includes subjects whose creatine kinase value at baseline was within the normal range.

RUTHERFORD: Conclusions

- AMG 145 administered every 4 weeks yielded rapid and substantial reductions in LDL-C in HeFH patients on statins with or without ezetimibe.
- Percentage reduction of LDL-C, *measured by ultracentrifugation*, was 43% and 55% in the AMG 145 350 mg and 420 mg dose groups, respectively, versus a 1% increase in the placebo group.
- The addition of AMG 145 SC Q4W to intensive lipid-lowering therapy reduced LDL-C in a dose-responsive manner.
- AMG 145 was well tolerated, with no notable difference in the AE profile relative to placebo.
- These results suggest that AMG 145 may offer a new effective treatment option to further reduce LDL-C in HeFH patients unable to achieve optimal LDL-C targets on current medications.

CIRCULATION

Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia
The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial

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